Hypersensitivity

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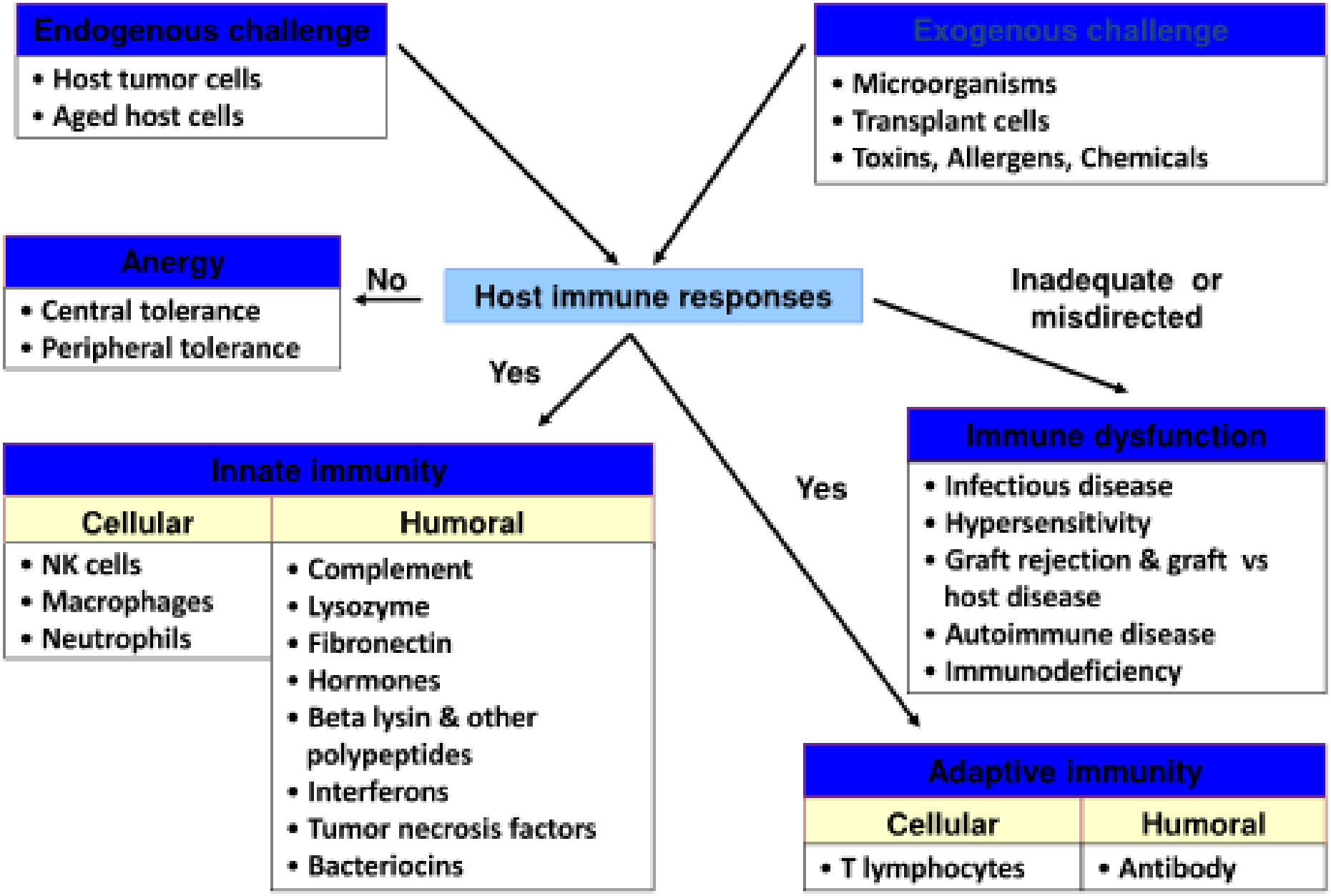
- In a adaptive immunity immune competent individual get defense against microbial diseases.
- The immune response is also capable of causing tissue injury and lead to disease.
- This immune response is termed as;

“Hypersensitivity”

OVERVIEW OF IMMUNE RESPONSES



- Hypersensitivity reactions could be caused by different sources;
  - Autoimmunity
    - Failure of self tolerance – one's own cells, tissues
    - 2-5% of population in developed countries
    - Incidence in rising
    - Common in 20-40 age group. More common in women than men.
  - Reaction against Microbes
    - Immune response against microbes.
    - T cell response against persistent microbes.
    - Resulting in severe inflammation , granuloma, tissue injury eg Tuberculosis granuloma
    - This antibody mediated – immune complex formation
  - Reaction against environmental antigens

- Reaction against environmental antigens
  - Most healthy individuals don't react against common harmless environmental substances
  - Almost 20% of population show abnormal response to one or more environmental substances
  - These individual produce abnormal quantities of IgE and cause allergic disease.
  - Some of the individuals become sensitized to environmental antigens and chemicals that contact to skin and their after cause T cell cytokine response.

Reasons of hypersensitivity reactions

- Defects or malfunction in either innate or acquired immune response provokes the illness or disease.
- Overactive immune response-Hypersensitivity.

  These individual produce abnormal quantities of IgE and cause allergic disease.
- Inappropriate reaction to self-autoimmunity
- Ineffective immune response-immuno-deficiency

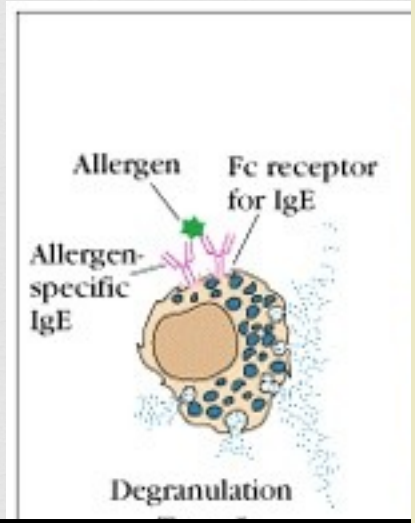
Types of Hypersensitivity Reaction

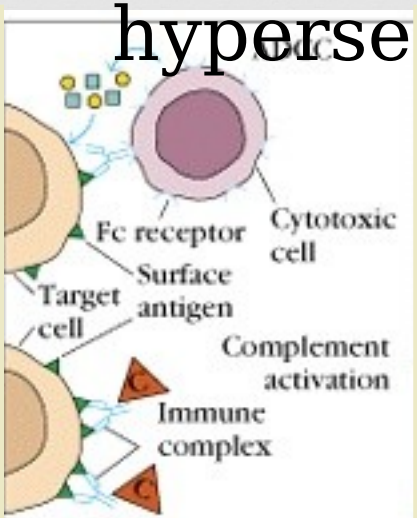
CLASSIFICATION OF HYPERSENSITIVITY

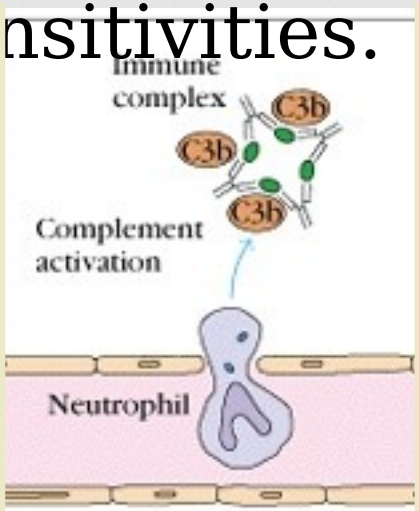
- In 1960s Gell and Coombs classified it into 4 types .

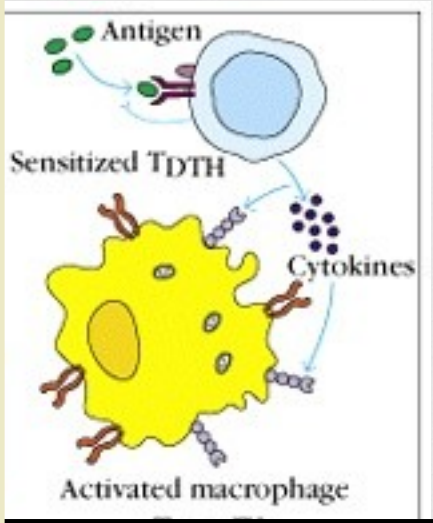
  - Type I – Immediate anaphylaxis
  - Type II – antibody – dependent cytotoxic hypersensitivity
  - Type III – Immune complex-mediated cytotoxicity
  - Type IV – delayed type hypersensitivity

Gel and Coombs classification of hypersensitivities.









Type I	Type II	Type III	Type IV
IgE Mediated	IgG/IgM Mediated	IgG Mediated	T cell
Classic Allergy	RBC lysis	Immune complex Disease	Delayed Type Hypersensitivity

- 1st exposure – sensitization
- 2nd exposure - shocking dose
- Anaphylaxis- without protection rather than an anamnestic (non forgetting) protective response.

- Anaphylaxis :
  - humoral immunity – immediate hypersensitivity
  - Cell- mediated immunity – delayed-type hypersensitivity.

TYPE I HYPERSENSITIVITY

CHARACTERISTICS:

- Occur quickly after 2 exposure to the antigen or allergen
- Inflammation reaction consists of accumulation of basophils, eosinophils,
- Neutrophils, Th_2 cells
  - T_h1 helper cells are the host immunity effectors against intracellular bacteria and protozoa (IL 12 → INF γ, IL 2).
  - T_h2 helper cells are the host immunity effectors against extracellular parasites including helminthes (IL 4, IL 2).
- IgE mediated response:
  - Antigens – plants, foods, drugs, insect products, mold spores, animal hair, Foreign serum, vaccines
- Atopy: the genetic predisposition to synthesize inappropriate levels of IgE specific for external

Allergens

TABLE 16-1 COMMON ALLERGENS ASSOCIATED WITH TYPE I HYPERSENSITIVITY

Proteins
- Foreign serum
- Vaccines

Plant pollens
- Rye grass
- Ragweed
- Timothy grass
- Birch trees

Drugs
- Penicillin
- Sulfonamides
- Local anesthetics
- Salicylates

Foods
- Nuts
- Seafood
- Eggs
- Peas, beans
- Milk

Insect products
- Bee venom
- Wasp venom
- Ant venom
- Cockroach calyx
- Dust mites

Mold spores

Animal hair and dander

In the US ---
36 million people
said to have hay fever!

Characteristics of allergens

- Small 15-40 kDa proteins.
- Specific protein components
  - Often enzymes.
- Low dose of allergen
- Mucosal exposure.
- Most allergens promote a Th_2 immune.

Allergens

Dermatophagoides pteronyssinus
(common dust mite)

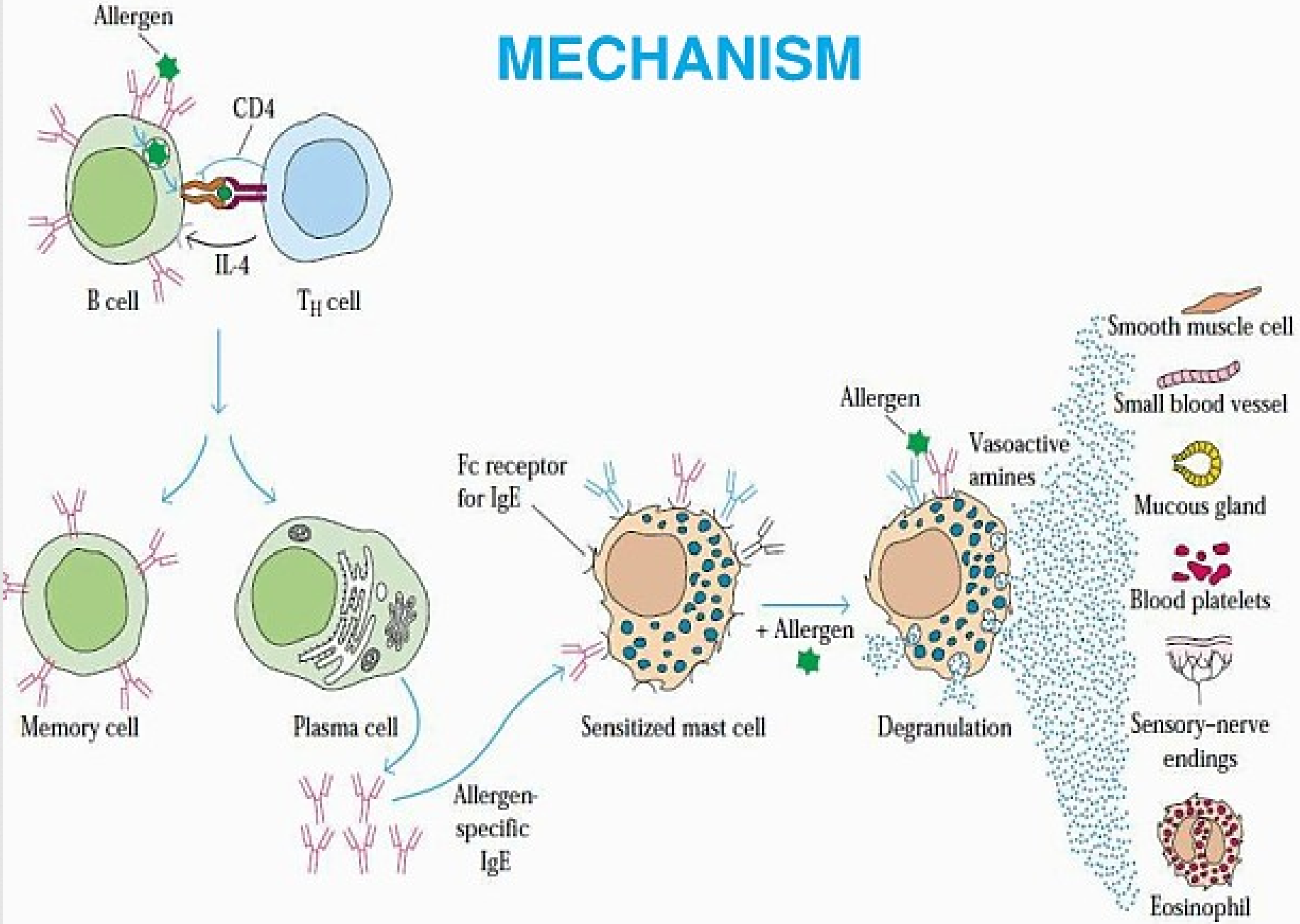
Example: Der P1

Der P1 is an enzyme allergen
from the fecal pellets of the dust mite.

Mediators of Type I Hypersensitivity
Immediate effects

- **Primary**
  - **Histamine -** an organic nitrogenous compound involved in local immune responses,
    - Constriction of smooth muscles.
      - Bronchiole constriction = wheezing.
      - Constriction of intestine = cramps-diarrhea.
    - Vasodilation with increased fluid into tissues causing increased swelling or fluid in mucosa.
    - Activates enzymes for tissue breakdown.
- **Secondary**
  - **Leukotrienes -** Leukotrienes are a family of eicosanid inflammatory mediators produced in leukocytes by the oxidation of arachidonic acid (AA)
  - **Prostaglandins (PG) -** a group of physiologically active lipid compounds having diverse hormone-like effects in animals.
  - **Serotonin -** Serotonin is found in preformed state in mast cells and
  - platelets.It causes vasoconstriction, increased capillary permeability and smooth muscle contraction**.**
  - **Th_2 cytokines** – IL 4, IL 5, IL 13, GM-CSF

MECHANISM



Busse and Lemanske NEJM Feb 2001; 344:350

Treatment for Type I

- Drugs.
  - Non-steroidal anti-inflammatories
  - Antihistamines – block histamine receptors.
  - Steroids
  - Theophylline OR epinephrine – prolongs or increases cAMP levels in mast cells which inhibits degranulation.
- Immunotherapy
  - Desensitization (hyposensitization) also known as allergy shots.
  - Repeated injections of allergen to reduce the IgE on Mast cells and produce IgG.

CONT.
H. DUST
MITE
GRASS
SHRUB
TREE

TYPE II Hypersensitivity

Antibody Mediated Cytotoxicity

TYPE III Hypersensitivity

Antigen antibody immune complexes.
IgG mediated

Immune Complexes

- PMNs and macrophages bind to immune complexes via FcR and phagocytize the complexes.

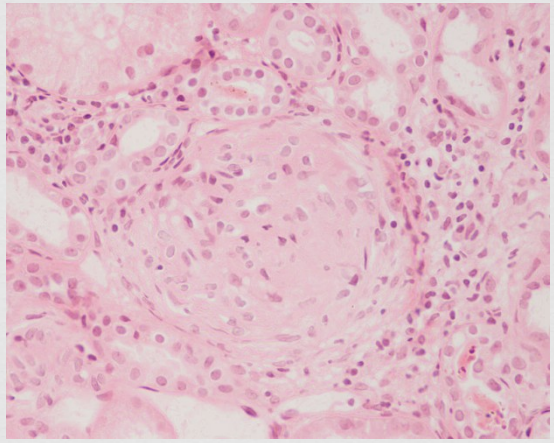
BUT

- If unable to phagocytize ("Frustrated Phagocytes“) the immune complexes can cause inflammation via Complement activation.
  - The Frustrated Phagocytes cells will degranulate in the area of immune complex deposition and trigger inflammation.
  - Unable to eat -------try to digest outside cell.

TYPE III

- Deposited in joints causing local inflammation = **Arthritis**.

- Deposited in kidneys = **Glomerulonephritis**



TYPE III

Immune Complex Disease

- Serum sickness from large amounts of antigen such as injection of foreign serum.
- Serum sickness is usually transient immune complex disease with removal of antigen source.

TYPE IV Delayed Type Hypersensitivity

Th_1 cells and Macrophages

- DTH response is from:
  - Th1 cells release cytokines to activate macrophages causing inflammation and tissue damage.
  - Continued macrophage activation can cause chronic inflammation resulting in tissue lesions, scarring, and granuloma formation.
- Delayed is relative because DTH response arise 24-72 hours after exposure rather than within minutes.

TYPE IV Delayed Type Hypersensitivity

Th_1 cells and Macrophages

Stages of Type IV DTH

Primary Sensitization stage

- Memory Th_1 cells against DTH antigens are generated by dendritic cells during the sensitization stage.
- These Th_1 cells can activate macrophages and trigger inflammatory response.
- Secondary Sensitization / Contact
- This yields what we call DTH.
- Th1 memory cells are activated and produce cytokines.
  - IFN-γ, TNF-α, and TNF-β which cause tissue destruction, inflammation.
  - IL-2 that activates T cells and CTLs.
  - Chemokines – for macrophage recruitment.
  - IL-3, GM-CSF for increased monocyte/macrophage

Stages of Type IV DTH

Effector stage

Secondary exposure to antigen

- Inflamed area becomes red and fluid filled can form lesion.
  - From tissue damage there is activation of clotting cascades and tissue repair.
- Continued exposure to antigen can cause chronic inflammation and result in granuloma formation.
- Example: **Contact dermatitis**

Contact dermatitis

Delayed type hypersensitivity (DTH)

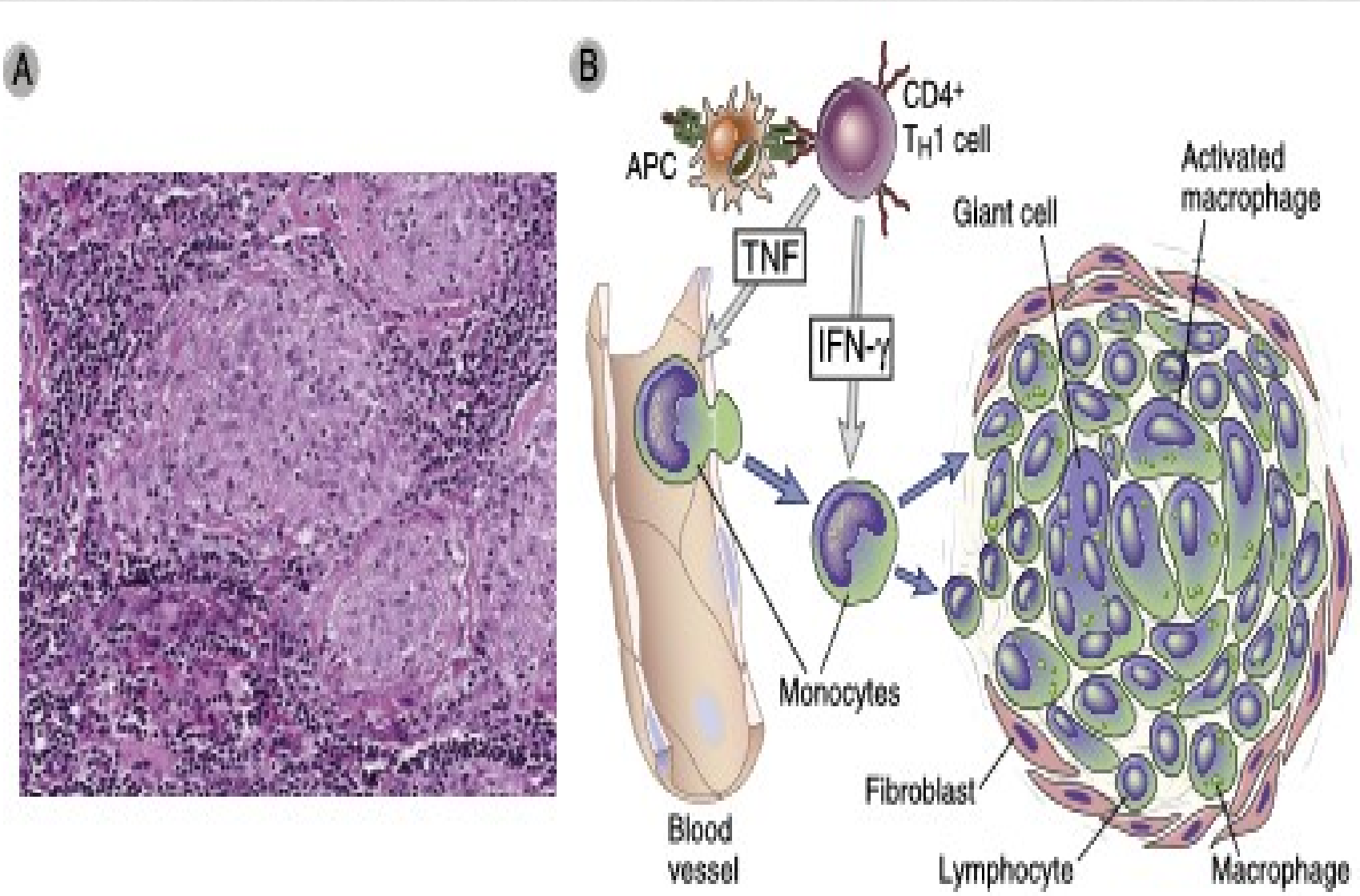
TABLE 14-3 INTRACELLULAR PATHOGENS AND CONTACT ANTIGENS THAT INDUCE DELAYED-TYPE HYPERSENSITIVITY

Intracellular bacteria	Intracellular viruses
Mycobacterium tuberculosis	Herpes simplex virus
Mycobacterium leprae	Variola (smallpox)
Listeria monocytogenes	Measles virus
Brucella abortus	Contact antigens
Intracellular fungi	Picrylchloride
Pneumocystis carinii	Hair dyes
Candida albicans	Nickel salts
Histoplasma capsulatum	Poison ivy
Cryptococcus neoformans	Poison oak
Intracellular parasites	
Leishmania sp.	

DTH is a type of immune response classified by **Th1 and macrophage** activation that results in tissue damage.

DTH can be the result of

Granuloma Formation from DTH Mediated by Chronic Inflammation



Drug reactions can be any Type of Hypersensitivity

TABLE 16-5 Penicillin-induced hypersensitive reactions

Type of reaction	Antibody or lymphocytes induced	Clinical manifestations
I	IgE	Urticaria, systemic anaphylaxis
II	IgM, IgG	Hemolytic anemia
III	IgG	Serum sickness, glomerulonephritis
IV	T_{DTH} cells	Contact dermatitis